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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/835,126	04/16/2001	Randolph J. Noelle	20052/1200522-US1	4674

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EXAMINER	
GAMBEL, PHILLIP	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 03/24/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/835,126	Applicant(s) NOELLE ET AL.	
	Examiner Phillip Gambel	Art Unit 1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on 04 February 2005.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1,2, 4-11, 3-15 is/are pending in the application.

4a) Of the above claim(s) 14 and 15 is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1,2,4-11 and 13 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

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DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office Action has been withdrawn pursuant to 37 CFR 1.114.

Applicant's submission, filed on 2/4/05, has been entered.

Applicant's amendment, filed has been entered.

Claims 1, 4, 6, 8, 10 and 13 have been amended.

Claim 3 has been canceled. Claim 12 has been canceled previously.

Claims 1, 2, 4-11 and 13 are being acted upon as the elected invention with respect to anti-gp39 antibodies as the gp39 antagonist, transplantation as the disease and assaying for IL-2.

Claims 14-15 have been withdrawn as being drawn to the non-elected species.

2. The text of those sections of Title 35 USC not included in this Action can be found in a prior Action.

This Action will be in response to applicant's arguments, filed 2/4/05.

The rejections of record can be found in the previous Office Actions.

Applicant's arguments and the examiner's rebuttal are essentially the same of record.

3. The previous objection to the amendment filed 9/22/03 under 35 U.S.C. 132 because it introduces new matter into the disclosure with respect to the disclosure of "5,876,718" in the paragraph beginning on page 8, line 22, has been obviated by applicant's amendment, filed 2/4/05.

4. Claims 1, 2, 4-11 and 13 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Noelle et al. (U.S. Patent No. 5,876,718) in view of the art known use of irradiating antigen presenting cells at the time the invention was made, as evidenced by Rooney et al. (U.S. Patent No. 5,962,318) and in view of the art known culturing of donor T cells for treatments over varying lengths of time, as evidenced by Riddell et al. (J. Immunol. Methods 128: 189-201) and monitoring the induction of T cell non-responsiveness ex vivo, as taught by Sykes et al. (U.S. Patent No. 6,006,752) essentially for the reasons of record.

Applicant's arguments, filed 2/4/05, have been fully considered but are not found convincing essentially for the reasons of record.

Applicant's arguments and the examiner's rebuttal are essentially the same of record.

Applicant argues that the amended claims are unobvious over the combination of references since they do not teach or suggest all the limitations of the presently claimed invention, there is no motivation to combine these references and, at best, they provide an "obvious to try" situation.

In contrast to applicant's assertions that Noelle et al. is limited to in vivo treatment of the recipient with GVHD and that Noelle et al. does not teach in vitro or ex vivo treatment of cells and in fact teaches in vitro treatment of recipient with GVHD with anti-gp39 antibody is ineffective, the following is noted.

In contrast to applicant's assertions, Noelle et al. is not limited to in vivo administration of anti-gp39 antibodies. For example, column 11, paragraph, column 11, paragraph 1 of the Noelle et al. discloses that: "In a case where the cells to be administered are bone marrow cells, wherein inhibition of GVHD is desired, donor T cells in the bone marrow can be tolerized before transfer to the recipient host by incubating the donor bone marrow with B cells from the host and a gp39 antagonist in vitro."

Therefore applicant's basic premise that Noelle et al. did not teach ex vivo manipulation of cell populations prior to transplantation or prior to administering anti-gp39 antibodies in vivo is not consistent with the clear teachings of Noelle et al. and, in turn, applicant's basis for obviating the teachings of the primary reference is without foundation.

Noelle et al. teach inducing T cell non-responsiveness to desired alloantigens with gp39 antagonists, including the use of anti-gp39 antibodies (i.e. anti-CD40L antibodies) (gp39 Antagonists) and antigen presenting cells, including bone marrow and peripheral bloods cells (Cells of Induction of Antigen-Specific Tolerance), for transplantation, including bone marrow transplantation, including before transfer to the transplant recipient in vitro (Administration of Cells and gp39 Antagonists) (see entire document, including Detailed Description of the Invention). Although Noelle et al. does not mention mixed lymphocyte reaction per se, it would have readily apparent to the one of ordinary skill in the art at the time the invention was made that a mixed lymphocyte reaction was accomplished by carrying out the above-mentioned procedures. Transplantation including bone marrow transplantation are provided to recipients in need of immune reconstitution as a result of disease or disease treatment.

Although Noelle et al. is silent about the particular time ranges set recited in the instant claims 6-7 per se, one of ordinary skill would have immediately envisaged at the time the invention was made that the culture of donor T cells would have fallen into such ranges (e.g. 1, 3, 5 days), as known typical days of culturing T cells at the time the invention was made, including the Examples set forth in Noelle et al.

In contrast to applicant's assertions concerning the purposes of the Riddell et al. reference, Riddell et al. was provided simply to teach the growth and expansion of antigen-specific T cells in culture for up to three months that can be employed for therapeutic use (see entire document).

Riddell et al. was not relied upon for teaching adoptive transfer of T cells to induce an immune response in transplant recipients, who are targeted for transplantation tolerance while the patients described in Riddell are being treated for diseases with T cells specific for said diseases.

Whether the endpoints of using T cells in patient populations may be different, Riddell et al. is consistent with the teachings of Noelle et al. in the growth and expansion of T cells in culture for therapeutic use.

Applicant has not contradicted the ability of the ordinary artisan to grow and expand T cells of interest by the ordinary artisan at the time the invention was made.

Given the desired endpoint of nonresponsiveness, the ordinary artisan would have expected to culture the donor T cells, antigen presenting cells with gp39 antagonists for various times, including those encompassed by the claimed invention to achieve the desired endpoint.

Similarly, while applicant argues that Rooney et al. is drawn to stimulating immune responses to antigens of interest in adoptive immunotherapeutic regimens, again Rooney et al. was provided simply to address some of the basic principles and practices of cell culture and manipulation in the art at the time the invention was made, and perhaps for the past 20 years at least.

Again, whether the endpoints of using T cells in patient populations may be different, Rooney et al. is consistent with the teachings of Noelle et al. in the growth and expansion of T cells in culture for therapeutic use and the manipulation of antigen presenting cells.

In contrast to applicant's assertions, antigen presenting cells for a variety of immunological processes were routinely irradiated at the time the invention was made to alleviate the activity of other cell types including T cells given that antigen presentation was still provided, as evidenced by Rooney et al. (e.g. see columns 14-15, overlapping paragraph and Examples 1-3 in columns 20-36).

Again, it is noted that Noelle et al. teach depleting antigen presenting cells of T cells (see column 10, paragraph 2).

Applicant has not contradicted the ability of irradiation, which applicant admits prevents the proliferation of non-specific cells, to deplete T cells. If the irradiated T cells cannot divide, T cells will be depleted via irradiation.

Applicant has not contradicted nor distinguished this decades-old practice of irradiated antigen presenting cells between the prior art and the instant methods.

While applicant argues that Sykes is limited to teaching testing recipient rather than donor cells for the effects of tolerance induction, Noelle et al. does clearly teach methods to tolerize T cells in vitro with a gp39 antagonist to affect contact dependent helper effector function (e.g. column 6, paragraph 5, column 11, paragraph 1and column 13, paragraph 3) and the Examples do exemplify various assays to monitor the induction of T cell tolerance (See Examples on columns 29).

Again, Sykes et al. simply provides teaching determining the ability of a treated T cell to release a cytokine such as IL-2 to determined the effect of an immunosuppressive drug (see entire document, particularly, column 10, paragraphs 5-6)

The various methods of testing the induction or responsiveness of T cells to regimens that induce tolerance or antigen-specific non-responsiveness were applicable to testing T cells whether the ordinary artisan was testing the donor or recipient T cells in methods of transplantation or whether the ordinary artisan was testing T cells in any of a variety of methods or assays to test the responsiveness of T cells of interest.

In particular, IL-2 has been a standard measure of T cell activity for decades by the ordinary artisan, whether one was measuring stimulation or suppression of T cell responses.

Applicant's arguments in conjunction with Exhibit A are not found convincing of unexpected results in view of the clear motivation and expectation of success in inducing T cell specific non-responsiveness both via ex vivo as well as in vivo manipulations

A prior art reference may be considered to teach away when "a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant." See In re Gurley, 31 USPQ2d 1130, 1131 (Fed. Cir. 1994).

Here, in contrast to applicant's assertions, the prior art primary reference of Noelle et al. is clearly drawn to the same or nearly the same methods to achieve the same endpoints as the current claimed methods. The secondary references simply filled in well -practiced and established methods of manipulating and testing immune cells, particularly T cell – antigen presenting cell interactions. There is no discouragement nor skepticism in the prior art for the ex vivo manipulation of donor and recpieint cell populations to achieve antigen specific non-responsiveness in transplantation regiments at the time the invention was made.

Once a prima facie case of obviousness has been made the burden of going further is shifted to applicant. In re Keller, 642 F.2d 4B, 208 USPQ 871, 882 (CCPA 1981). This applicant has not done, but rather argues the references individually and not their combination. One cannot show non-obviousness by attacking references individually where the rejections are based on a combination of references. In re Young 403 F.2d 759, 150 USPQ 725 (CCPA 1968). See MPEP 2145.

In response to applicant's arguments that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See In re Fine 5 USPQ2d 1596 (Fed. Cir 1988) and In re Jones 21 USPQ2d 1941 (Fed. Cir. 1992).

In this case, the teachings of the primary reference Noelle et al. pertaining to the difficulties in inducing antigen-specific non-responsiveness by manipulating donor and host immune cell populations as well as methods to accomplish such goals coupled with the teachings of secondary references in providing for well-established culture conditions and manipulation in generating specific cell interactions and endpoints would have led the ordinary artisan to solve the same a well known problem in the art by combining the references. The strongest rationale for combining reference is a recognition, expressly or implicitly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent that some advantage or expected beneficial result would have been produced by their combination In re Sernaker 17 USPQ 1, 5-6 (Fed. Cir. 1983) see MPEP 2144

The test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference and not is it that the claimed invention must be expressly suggested in any one or all of the references; but rather the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. In re Keller, 642 F.2d 413, 208 USPQ 871 (CCPA 1981). See MPEP 2145.

Given the teachings of the references, one of ordinary skill in the art at the time the invention was made would have been motivated to culture donor T cells in vitro under certain conditions and times encompassed by the claimed limitations with a gp39 / CD40 ligand antagonist such as anti-gp39 antibodies to induce antigen-specific unresponsiveness in the donor T cells populations prior to transplantation for treating various human conditions and diseases. Given the teachings of Noelle et al. and Sykes et al., one of ordinary skill in the art would have been motivated to monitor the effectiveness of the induction of T cell non-responsiveness or tolerance by treating T cells with the gp39 antagonist anti-gp39 antibodies by monitoring various parameters of T cell function, including monitoring the elaboration of cytokines, including IL-2. From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Applicant's arguments have not been found persuasive.

5. No claim is allowed.

6. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (571) 272-0844. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841.

The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Phillip Gambel, PhD.
Primary Examiner
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March 21, 2005